REMARKS

Claims 24-27, 36-44, 47, 52, 55-59, 98 and 99 are pending. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Applicant respectfully requests further consideration of the present application in light of the following remarks.

All of the prior rejections have been maintained. Thus, claims 24-26, 36-38, 44, 47, 52, and 55-57, and now claims 98 and 99, are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and Li *et al.* Claims 24-27, 36-38, 44, 52, and 55-57, and now claims 98 and 99, are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,106,955. Claims 24-26, 36-42, 44, 52, and 55-57, and now claims 98 and 99, are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,686,072 and PCT publication WO 95/09917. Claims 24-26, 36-39, 44, 52, 55-57, 60-70, 73-77, 91-93, and now claims 98 and 99, are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and European Patent Application No. 510949. Claims 24-27, 36-38, 43, 44, 52, and 55-89, and now claims 98 and 99, are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,698,178. Claims 24-27, 38, 43, 44, 52, 55-89, and now claims 98 and 99, are rejected under 35 U.S.C. §103(a) based on WO 96/04925 in view of Maloney *et al.* and United States Patent No. 5,698,178.[1]

All of the arguments made previously with respect to these rejections are incorporated by reference here. In response to applicant's arguments with respect to *In re Kerkhoven*, the examiner replies that "the teachings of both documents reasonably establish motivation to combine the two antibodies for a method of treatment, especially in light of their success in individual treatments." In making this statement, the Examiner has not addressed applicant's discussion of the distinctions to be drawn between the facts of *Kerkhoven* and the present facts, particularly with respect to the nature/predictability of the

[1] It is noted that the last three rejections include claims that have been cancelled for quite some time.

art. As noted, even MPEP 2144.06, which is cited by the examiner, cautions that obviousness of a combination of compositions taught by the prior art to be useful for the same purpose does not always hold, citing *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been *prima facie* obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive.... Appellant argues... hindsight reconstruction or at best... 'obvious to try'.... We agree with appellant."). Thus, it is apparent that the Office cautions examiners to determine whether it is obvious to combine two compositions on a ***case-by-case*** basis.

Moreover, applicant has provided the declarations of three experts in the area of immunotherapy, regarding the absence of motivation to combine the two antibodies for a method of treatment as presently claimed. The declarants attest that even single antibody therapy was not conventional circa 1998, let alone therapy with a combination of antibodies, and that Maloney did not suggest to them that they could extend Maloney's teaching to combinations of anti-CD20 and anti-CD22 antibodies. For all of these reasons, the teaching of *Kerkhoven* is inapplicable in the present context and therefore the present claims are believed to be allowable over the references cited in the outstanding rejections.

Finally, applicant has made of record evidence that the present combination of antibodies produces results that are unexpected. This evidence was in the form of several articles. Even assuming, *arguendo*, the present combination was somehow suggested, the evidence or record clearly rebuts the examiner's conclusion of obviousness.

With respect to the articles submitted by applicants, the examiner comments that "the papers submitted by Applicants all set forth epratuzumab as the CD22 antibody used in combination with CD20 antibody, rituximab or IMMU-106. The prior art teaches LL2 monoclonal antibody, which is distinct from the CD22 antibody listed in Applicant's supporting references…arguments based on these papers are not commensurate." "LL2 monoclonal antibody" is the term generally used to refer to the murine monoclonal antibody previously known as EPB2 (see background of US 5,789,554, the "prior art" referenced by the examiner). US 5,789,554, on the other hand, focuses on chimerized

and humanized LL2 antibodies denoted cLL2 (mouse/human chimeric mAb) and hLL2 (humanized mAb), respectively, which include the CDRs of murine monoclonal antibody LL2. The statement that the prior art teaches LL2 monoclonal antibody, which is distinct from the CD22 antibody listed in Applicant's supporting references is inaccurate. The prior art teaches cLL2 and hLL2, and mentions LL2 in its background and as a source of the CDRs for the cLL2 and hLL2.

Epratuzumab is humanized LL2 (hLL2). Accordingly, the proffered articles which show the unexpected results that are achieved with the present combination of antibodies are a comparison to "the prior art" and are not a comparison to an antibody that is "distinct" from the antibody of applicant's claims. The examiner has not provided any rationale why unexpected results achieved with a combination employing hLL2 would not extend to the chimeric LL2 antibodies of US 5,789,554. Nor has the examiner explained why the results are not commensurate in scope with a claim that recites anti-CD22 antibodies. The examiner also has not separately addressed claim 44, which recites that the anti-CD22 antibody is hLL2.

The comparison provided by the articles is a comparison to the claimed and more favored embodiment in US 5,789,554, *i.e.*, the humanized antibody as opposed to the chimeric antibody. It is thus a comparison that is commensurate in scope with both the alleged *prima facie* case and the present claims.

Finally, applicant wishes to expand upon the relationship between Dr. Goldenberg and each of the three declarants, in light of *Nilssen v. Osram Sylvania*, 504 F.3d 1223 (Fed.Cir. 2007), which was decided after the declarations were submitted. Dr. Foon has known Dr. Goldenberg of Immunomedics and the Garden State Cancer Center for many years as a researcher in the field, and they interact at meetings. Dr. Foon also visited with Dr. Goldenberg at the Garden State Cancer Center in New Jersey on one occasion about 5 or so years ago. Dr. Leonard is a long-term colleague of Dr. Goldenberg, and has co-authored several clinical papers involving epratuzumab with Dr. Goldenberg. Dr. Leonard also has been principal investigator on three studies for Immunomedics, and has received some small consulting fees for time spent with interested companies reviewing Immunomedics' products. A few years ago, Dr. Czuczman's research group became a subcontractor on a grant awarded to Garden State Cancer Center, where Dr. David

Goldenberg is Program Director. The grant involved laboratory studies on antibody therapies of lymphomas. Dr. Czuczman also published an article with Dr. Goldenberg in 2003 on radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-DOTA humanized anti-CD22 IgG (^{90}Y-Epratuzumab), when they collaborated on a GSCC clinical trial, funded by the National Cancer Institute.

If there are any problems with this response, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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